PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/IB2004/004159	International filing date *(day/month/year)* 13.12.2004	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or national classification and IPC A61K47/12, A61K47/26, A61K38/27		
Applicant PHARMACIA CORPORATION		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.06.2005	15.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hedegaard, A Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/004159

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-25 as originally filed

Claims, Numbers

1-15 as originally filed

Drawings, Sheets

1/7-7/7 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11-15
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Section V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1 = US-A-6 593 296
   D2 = US-A- 5 206 219
   D3 = US 2003/0162711 A

   If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

   D1 discloses aqueous formulations comprising growth hormone, buffer (pH 5.0-7.5), and a single stabilizing agent or a combination of two or more thereof. Said stabilizing agents are selected from polyoxyethylene-polyoxypropylene block copolymer non-ionic surfactants (Pluronics), taurocholic acid and methylcellulose derivatives.

   D2 (see example 3) discloses an aqueous formulation comprising among other ingredients growth hormone (1.83%), phosphate buffer (pH 7.5 -7.8), polyethylene glycol 400 (23.53%) and Tween 80 (2.95%).

   D3 (see the examples) discloses aqueous formulations comprising among other ingredients growth hormone, L-histidine buffer (pH 5-7), and non-ionic surfactant (Pluronic or Lutrol). In paragraph [0068] it is mentioned that polyethylene glycol can be added as excipient.

2. The subject-matter of claim 1 is not novel (Art. 33(2) PCT) over D1-D3 (see above under item 1).

   With respect to D1 it is pointed out that Pluronics and methylcellulose derivatives can be characterised as non-ionic surfactants as well as stabilising polymers. Hence, when selecting two stabilising agents from the group of polyoxyethylene-

polyoxypropylene block copolymer non-ionic surfactants (Pluronics), taurocholic acid and methylcellulose derivatives as defined in D1 there will always be a non-ionic surfactant and a polymeric stabilizer selected.

3. The subject-matter of independent claim 11 is novel (Art. 33(2) PCT) since the combination of ingredients in the specified amounts and with the specified pH has not been disclosed in the available prior art.

4. The subject-matter of independent claim 11 only differs from D2 in that it specifies the amount of PEG to be from "about 0.001% to about 20%" (see however below in Section VIII). Such a modification does not appear to be accompanied by any non-obvious effect (the compositions according to D2 are also stable) and can be carried out by the skilled person without having to resort to inventive skill. Therefore, the subject-matter of claim 11 is not considered to involve an inventive step (Art. 33(3) PCT).

   With respect to inventive step the attention is also drawn to D1 which discloses that the addition of one or two stabilising agents selected from non-ionic surfactants and polymeric stabilisers improves stability of buffered solutions comprising growth hormone when subjected to prolonged storage over a range of temperatures, including below freezing and above freezing.

5. A positive international preliminary report for the subject-matter of the dependent claims can only be established when they refer to independent claims which meet the requirements of the PCT.

Re Section VIII

Certain observations on the international application

1. The word "about", particularly when applied to a range, detracts from the general clarity and should be deleted throughout the description and claims (Art. 6 PCT).